CLAIMS

1. A method for identifying compounds capable of depleting mast cells, wherein said compounds are non-toxic for other hematopoeitic cells that are not mast cells or related cells or cell lines or derived cell lines thereof, such as SCF independent expanded human normal CD34+ cells, comprising the steps consisting of :

a) culturing mast cells in vitro in a suitable culture medium,

b) adding to said culture medium at least one candidate compound to be tested and incubating said cells for a prolonged period of time,

c) measuring the extent to which said compounds promote mast cells death or disrupt, interfere with, or inhibit mast cells growth, and selecting compounds for which mast cells depletion is observed,

d) identifying a subset of compounds selected in step c) that are unable to promote significant death of a cell chosen from other hematopoeitic cells that are not mast cells or related cells or cell lines or derived cell lines thereof, such as SCF independent expanded human normal CD34+ cells.

2. A method for identifying compounds capable of depleting mast cells, wherein said compounds are non-toxic for other hematopoeitic cells that are not mast cells or related cells or cell lines or derived cell lines thereof, such as SCF independent expanded human normal CD34+ cells, comprising the step consisting of :

a) providing a culture of mast cells, wherein said mast cells are selected from wild type mast cells and cell lines derived thereof, activated mutant mast cell lines, and activated wild type mast cells and cell lines derived thereof,

b) contacting the culture of said cells with at least one candidate compound under conditions allowing growth and/or survival of mast cells, measuring the level of cell death in the presence of the candidate compound; and comparing the level of cell death

in the presence of the candidate compound to the level of cell death in the absence of the candidate compound, wherein an increase in the level of cell death in the presence of the candidate compound is indicative of the mast cells depletion ability of the candidate compound,

c) providing a culture of at least one cell other than mast cells, wherein said cell is selected from hematopoeitic cells that are not mast cells or related cells or cell lines or derived cell lines thereof, such as SCF independent expanded human normal CD34+ cells,

d) contacting the culture of said cells with at least one compound identified in step b) under conditions allowing growth and/or survival of the cell depicted in step c), measuring the level of cell death in the presence of said compound; and comparing the level of cell death in the presence of the compound to the level of cell death in the absence of the compound, wherein no significant increase in the level of cell death in the presence of said compound is indicative of mast cells depletion specificity of said compound versus at least another hematopoeitic cell.

3. A method according to claim 1 or 2, wherein mast cells are chosen from isolated mast cells and cell lines derived thereof, BaF3, IC-2 mouse cells, HMC-1, P815 available at ATCC under the accession number TIB-64 , 10P2 available at ATCC under the accession number CRL-2034, 10P12 available at ATCC under the accession number CRL-2036, 11P0-1 available at ATCC under the accession number CRL-2037, and cell lines derived thereof .

4. A method according to one of claims 1 to 3, wherein other hematopoeitic cells that are not mast cells or related cells or cell lines are selected from the group consisting of human T lymphocyte Jurkat cell line (ATCC N° TIB-152 and cell lines derived thereof), the human B lymphocyte Daudi or Raji cell line (ATCC N° CCL-213 and CCL-86 respectively and cell lines derived thereof), the human monocytic U 937 cell line (ATCC

N° CRL-1593.2) and the human HL-60 cell line (ATCC N° CCL-240), cell lines derived thereof ATCC N° CRL-2258 and CRL-2392) and normal human CD34+ cells that are expanded in a culture medium comprising a cocktail of cytokine except SCF.

5. A method according to one of claims 1 to 4, wherein compounds capable of depleting specifically mast cells at a concentration below 10 μM, preferably below 1 μM are selected.

6. A method according to one of claims 1 to 5, wherein the compounds exhibiting Ratios E/S ranging from 1/1000 to 1/5 are selected.

7. A method according to one of claims 1 to 6, wherein the cell death assay further comprises a cell proliferation assay, a cell viability assay and/or an apoptosis assay.

8. A method according to one of claims 1 to 6, wherein the extent of cell death is measured by 3H thymidine incorporation, the trypan blue exclusion method, using propidium iodide or by the ^{51}Cr-release assay.

9. A method according to one of claims 1 to 6, wherein the extent of cell death is determined by a test of intracellular esterase activity, and a test of plasma membrane integrity, preferably using fluorescent calcein and ethidium homodimer-1.

10. A method according to one of claims 1 to 6, wherein the extent of cell death is determined by discriminating between living and dead cells using $DiOC_{18}$ and propidium iodide.

11. A method according to one of claims 1 to 10, wherein the extent of cell death is measured by fluorometric assays of cell viability and cytotoxicity using a fluorescence microscope, a fluorometer, a fluorescence microplate reader or a flow cytometer.

12. A method according to one of claims 1 to 11, wherein the mast cells that are IL-3 dependent cells are cultured in a culture media comprising IL-3 at a concentration comprised between 0.5 and 10 ng/ml, preferably between 1 to 5 ng/ml.

13. A method according to one of claims 1 to 12, wherein compounds to be tested are selected from inhibitors of tyrosine kinases, such as Akt, c-Cbl, CRKL, Doc, p125 Fak, Fyn, Grap, Jak2, Lyn, MAPK, MATK, PI3-K, PLC-γ, Raf1, Ras, SHP-1, SHP2 (Syp), Tec, Vav and Flt-3.

14. A screening method according to one of claims 1 to 12, wherein said compounds are selected from the group consisting of indolinone, pyrimidine derivatives, pyrrolopyrimidine derivatives, quinazoline derivatives, quinoxaline derivatives, pyrazoles derivatives, bis monocyclic, bicyclic or heterocyclic aryl compounds, vinylene-azaindole derivatives and pyridyl-quinolones derivatives, styryl compounds, styryl-substituted pyridyl compounds, , seleoindoles, selenides, tricyclic polyhydroxylic compounds and benzylphosphonic acid compounds.

15. A compound obtainable by the method according to one of claims 1 to 12, wherein said compound is capable of depleting mast cells and has no significant toxicity for other hematopoietic cells, preferably compounds having an E/S ratio ranging 1/1000 to 1/5.

16. Use of a compound according to claim 15 to manufacture a medicament.

17. A method for treating a disease selected from autoimmune diseases, allergic diseases, bone loss, tumor angiogenesis, inflammatory diseases, inflammatory bowel diseases (IBD), interstitial cystitis, mastocytosis, infections diseases, and CNS disorders comprising administering a compound obtainable from a method according to one of claims 1 to 14 to a mammal in need of such treatment.

18. A method for promoting hair growth and hair color revival comprising administering a compound obtainable from a method according to one of claims 1 to 14 to a human need of such treatment.

19. A method according to claim 17 for treating multiple sclerosis, psoriasis, intestine inflammatory disease, ulcerative colitis, Crohn's disease, rheumatoid arthritis and polyarthritis, local and systemic scleroderma, systemic lupus erythematosus, discoid lupus erythematosus, cutaneous lupus, dermatomyositis, polymyositis, Sjogren's syndrome, nodular panarteritis, autoimmune enteropathy, proliferative glomerulonephritis, active chronic hepatitis and chronic fatigue syndrome.

20. A method according to claim 17 for treating graft-versus-host disease or graft rejection in any organ transplantation including kidney, pancreas, liver, heart, lung and bone marrow.

21. A method according to claim 17 for treating subepidermal blistering disorders such as aphthous ulcers, and several bullous diseases such as pemphigus, bullous pemphigoid and cicatricial pemphigoid.

22. A method according to claim 21 comprising further administering at least one antibiotic, preferably selected from dapsone, azathioprine, erythromycin, propionylerythromycin, neomycin, gentomycin, tobramycin, and mechlocycline.

23. A method according to claim 17 for treating asthma, allergic rhinitis, allergic sinusitis, anaphylactic syndrome, urticaria, angioedema, atopic dermatitis, allergic contact dermatitis, erythema nodosum, erythema multiforme, cutaneous necrotizing venulitis, insect bite skin inflammation and blood sucking parasitic infestation.

24. A method according to claim 17 for treating skin allergic disorders such as urticaria, atopic dermatitis, allergic contact dermatitis, erythema nodosum, erythema multiforme, cutaneous necrotizing venulitis, insect bite skin inflammation and blood sucking parasitic infestation especially in dogs and cats.

25. A method according to one of claims 23 and 24 wherein the compound is administered with aerosolized formulations to target areas of a patient's respiratory tract, intranasal or topical formulation.

26. A method according to claim 17 for treating tumor angiogenesis in human.

27. A method according to claim 17 for treating skin disorders in human associated with mastocytosis, notably cutaneous mastocytosis including urticaria pigmentosa, diffuse cutaneous mastocytosis, solitary mastocytoma and bullous, erythrodermic and teleangiectatic mastocytosis.

28. A method according to claim 17 for treating category IV mastocytosis including mast cell leukemia.

29. A method according to claim 17 for treating dog mastocytoma.

30. A method according to claim 17 for treating treating inflammatory bowel diseases (IBD), such as Crohn's disease, mucositis, ulcerative colitis, and necrotizing enterocolitis.

31. A method according to claim 17 for treating interstitial cystitis in human.

32. A method according to claim 17 for treating bacterial infections in mammalian, especially in human, preferably for the treatment of recurrent bacterial infections, resurging infections after asymptomatic periods such as bacterial cystitis.

33. A method according to claim 17 for treating FimH expressing bacteria infections such as Gram-negative enterobacteria including *E. coli*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Citrobactor freudii* and *Salmonella typhimurium*.

34. A method according to claim 29 or 30 comprising further administering at least one antibiotic selected bacitracin, the cephalosporins, the penicillins, the aminoglycosides, the tetracyclines, the streptomycins and the macrolide antibiotics such as erythromycin; the fluoroquinolones, actinomycin, the sulfonamides and trimethoprim.

35. A method according to claim 17 for treating bone loss such as osteoporosis, including post menopausal osteoporosis, senile osteoporosis, and glucocorticoid-induced osteoporosis, osteitis fibrosa cystica, renal osteodystrophy, osteosclerosis, osteopenia, osteomalacia, fibrogenesis-imperfecta ossium, and Paget's Disease.

36. A method according to claim 17 for treating inflammatory disorders such as rheumatoid arthritis, conjunctivitis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, polyarthritis, and other arthritic conditions as well as pain associated with these inflammatory diseases.

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